RENAL SIDE EFFECTS IN CHILDREN WHO HAVE COMPLETED TREATMENT FOR CHILDHOOD CANCERS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL, SOUTH AFRICA.

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Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in Medicine.

Johannesburg, 2014

DECLARATION

I, Dr Abdullahi Mudi declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Signature

10th day of November, 2014

Dedication

To all the children around the world with childhood cancers.

Abstract

Background: The causes of renal dysfunction in children treated for childhood cancers are multifactorial and clinical manifestations of dysfunction include hypertension, proteinuria and varying degrees of renal insufficiency. This study aimed to determine the different residual effects of cancer therapy on the renal system and factors associated with the residual effects in children treated for childhood cancers.

Patients and Methods: The study was a descriptive cross sectional study that assessed 130 children, between the age of 1 and 18 years, who had completed treatment at Charlotte Maxeke Johannesburg Academic Hospital and were being followed up at the paediatric oncology clinic of the hospital.

Results: After a median follow-up post treatment of 2 years, the various manifestations of renal dysfunction identified in the survivors included; decreased GFR, hypomagnesaemia, hypophosphataemia, proteinuria, haematuria and hypertension. In total, 34 survivors (26.15%) had at least one manifestation of renal dysfunction after completing treatment. The most prevalent manifestation of renal dysfunction detected was decreased GFR (17.69%). Hypomagnesaemia and hypophosphataemia were present in 8 (6.15%) and 6 (4.62%) of the survivors respectively. Patients who had renal dysfunction pre-treatment were three times more likely to have renal dysfunction post-treatment. Ifosfamide, Carboplatinum, and nephrectomy were significantly associated with a reduction in GFR

Conclusion: A significant number of the survivors had a decreased GFR while some of them had hypomagnesaemia and hypophosphataemia. There was a strong association between pre-treatment and post-treatment renal dysfunction. These findings are very important in terms of decision making for individual patients with respect to selecting treatment modalities and dosages and also with respect to instituting nephro-protective measures to avoid further damage to the kidneys during and after treatment.

Acknowledgement

I thank the Almighty for giving me the strength and guidance to conduct this study.

I would like to thank my supervisor and mentor, Dr Cecil Levy for his guidance and support in conducting this study. I also thank the staff of the paediatric renal unit for their support and understanding during the study period.

I wish to express my sincere appreciation to the staff of the Paediatric Oncology Clinic at CMJAH for their support during the period of the study, especially Professor J Poole and Dr J Geel. I also thank the survivors of childhood cancer and their parents for their participation in this study.

I am also grateful to the department of paediatrics for giving me the opportunity to go through with this degree.

Finally, a big thank you to my family back in Nigeria for their never ending support despite being far away.

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Nomenclature

1.	ARF	Acute Renal Failure
2.	BP	Blood Pressure
3.	CKD	Chronic Kidney Disease
4.	COG LTFU	Children's Oncology Group Long Term Follow Up
5.	CMJAH	Charlotte Maxeke Johannesburg Academy Hospital
6.	GFR	Glomerular Filtration Rate
7.	Gy	Gray
8.	HDMTX	High Dose Methotrexate
9.	MTX	Methotrexate
10.	NSAID	Non Steroidal Anti-Inflammatory Drug

1. INTRODUCTION

Cancer is a rare diagnosis in children. In well-resourced settings, the incidence of childhood cancer is 110 - 130 per million children per annum (1). Although the South African Children's Tumour Registry has reported an incidence of 600 - 700 new cases of childhood malignancies per year, in South Africa accurate figures for childhood cancer are not available (2). It is estimated that one in 600 children will develop cancer before they turn 16 years (3). Due to advances in both cancer therapy and supportive regimes, the prognosis for patients with cancer diagnosed under the age of 15 has improved dramatically over the past few decades (4). This has resulted in larger numbers of survivors who may now potentially present with long term side effects in greater numbers than seen before.

The renal system is just one of the systems in the body that may be affected as a result of cancer therapy. The causes of renal complications in children with cancer are multi-factorial. They may be due to the malignancy itself or may be secondary to the variety of treatment modalities used in treating these patients. These include the chemotherapy, radiotherapy or surgery used as the primary therapy or the supportive measures used to treat the inevitable complications of intensive chemotherapy (5,6). Common chemotherapeutic drugs implicated in causing nephrotoxicity include cisplatin, ifosfamide, high dose methotrexate and carboplatin (7-9).

Chemotherapy–induced nephrotoxicity may manifest as acute irreversible renal failure, slowly progressive chronic renal failure or as specific defects in renal tubule cell function

(10). Clinical manifestations of kidney damage include hypertension, proteinuria and varying degrees of renal insufficiency (11).

Assessment of childhood cancer survivors for late renal sequelae is aimed at detection of hypertension or other evidence of chronic renal injury. The Children's Oncology Group for Long Term Follow Up (COG LTFU) guideline recommends baseline screening for asymptomatic survivors of potentially nephrotoxic therapy. This includes measuring the blood pressure, baseline blood tests including calcium, magnesium and phosphate (CMP), urea and creatinine and performing a bedside urinalysis (7).

The finding of significant proteinuria on urinalysis will prompt concern about renal damage from prior therapy or the acquisition of new renal disease. Proteinuria is first detected by urinary dipstick, which primarily detects albumin. Abnormal glomerular filtration rate (GFR) is most often detected by elevated serum creatinine concentrations. Even mild elevations should be noted since as much as 50% of renal parenchymal loss may occur before detectable changes in the creatinine occur. Since early renal insufficiency is often asymptomatic, screening for proteinuria and or measurement of creatinine may be the only way to detect its presence (6,7).

Since potentially serious long-term renal sequelae may evolve following both single measures and additive nephrotoxic effects, long-term monitoring of growth, blood pressure, and renal function is mandatory for all paediatric oncology patients. These patients should also be counselled to avoid lifestyles that put them at risk for renal injury such as tobacco use, excessive non steroidal anti-inflammatory drug (NSAID) use, excessive alcohol consumption, and dehydration. In addition, avoidance of obesity and treatment of hyperlipidaemia will also offer some renal protective effects (6,7).

1.1 Literature Review

Childhood cancers are relatively rare and prognosis has been improving in the last three decades as a result of more accurate diagnoses and improved treatment strategies (2). During recent years the number of paediatric cancer survivors has considerably increased due to better treatment regimens and better supportive care (3). This has resulted in the long-term side-effects of the various cancer treatment regimens growing in importance. Several systems in the body may be affected including the renal system.

Various manifestations of renal dysfunction associated with anti – cancer treatment have been described in the past. The most documented manifestations include; hypertension, proteinuria, tubular dysfunction, and varying degrees of renal insufficiency in the form of reduced glomerular filtration rate (GFR) (6-14).

Frequencies of renal impairment in patients treated for childhood cancers have been documented in studies from various parts of the world but none reported from South Africa. In a single centre Iranian study, Arjmandi-Rafsanjani *et al* (13) reported a 25.2% rate of renal toxicity, including tubular disorders and hypertension. Similarly, Knijnenburg *et al* (14) reported a prevalence of 28.1% of therapy-related renal dysfunction in childhood cancer survivors. In both studies, the proportions reflected at least one renal adverse effect or elevated blood pressure (BP) in the survivors. Gronroos *et al* (12) documented a seven year follow up of 187 children post stem cell transplant in Finland and reported the finding of chronic kidney disease (CKD) in 41% at 1 yr, 31% at 3 yr, and 11% at 7 yr. In a retrospective study conducted by Bakr *et al* (8) in Egypt, the authors reported that about 10% of patients with acute kidney injury (AKI) developed CKD.

1.1.1 Mechanisms of nephrotoxicity

There are many possible reasons that the renal system may be affected after a course of cancer therapy. The primary disease may directly involve or infiltrate into the kidneys or related structures, and tumour lysis syndrome may result from the cancer or following treatment. Cancer treatments associated with renal damage later in life include chemotherapeutic drugs (ifosfamide, cisplatin, carboplatin, methotrexate), renal radiotherapy, and nephrectomy (7,12). Nephrotoxic supportive treatment like amikacin, vancomycin, amphotericin B and cyclosporin individually, or in addition to the cancer therapy, may cause renal damage (7,12).

Therapy induced nephrotoxicity can manifest as acute renal failure (perhaps even requiring some form of renal replacement therapy), slowly progressive chronic renal failure or as specific defects in renal tubule cell function (7). Clinical manifestations of kidney damage include hypertension, proteinuria and varying degrees of renal insufficiency (7).

In addition, children who undergo stem cell transplantation (SCT) may also develop acute renal impairment as a major side effect, often leading to permanent renal failure (15,16). Of course, it is often a combination of any, or all, of the above factors that will result in long term consequences for the renal system.

Primary disease

Kidney failure may result from primary tumours of the kidneys such as bilateral Wilms tumour or tumours of related structures such as the adrenal glands compressing on the renal parenchyma (8). Extra renal tumours compressing on the urinary flow system, or

tumours arising from the bladder such as rhabdomyosarcoma, may cause obstructive uropathy with resultant deleterious effects on renal function (8,17). Some tumours such as lymphomas and leukaemia may invade the renal parenchyma or cause renovascular obstruction leading to renal failure (8,17).

Tumour lysis syndrome (TLS)

Tumour lysis syndrome occurs when tumour cells release their contents into the bloodstream, either spontaneously due to rapid tumour cell turnover or due to chemotherapy-induced tumour cell lysis (18). Tumour lysis syndrome is seen commonly in cancers with a high potential for cell lysis such as high-grade lymphomas, acute leukaemia and other rapidly proliferating tumours leading to the characteristic findings of hyperuricaemia, hyperkalaemia, hyperphosphataemia, hypocalcaemia and, sometimes, acute renal failure (17,18). Acute renal failure usually occurs due to uric acid crystal formation in the renal tubules secondary to hyperuricaemia (uric acid nephropathy), calcium phosphate deposition related to hyperphosphataemia or a combination of both (18). Routine prophylaxis against TLS consists of oral or intravenous allopurinol to block uric acid formation coupled with intravenous hydration with or without urinary alkalinisation (8,17,18).

Chemotherapy

a. Ifosfamide

Ifosfamide (IFO) is an alkylating agent that is used in paediatric treatment protocols of lymphomas, rhabdomyosarcoma, soft tissue sarcomas, Wilms tumour, bone sarcomas, germ

cell tumours and neuroblastoma (12). The most common manifestation of ifosfamide-induced nephrotoxicity is proximal tubular dysfunction and, less often, decreased GFR (7,19). It may lead to the Fanconi Syndrome including hypophosphataemic rickets and proximal renal tubular acidosis. Ifosfamide may also cause any combination of chronic glomerular, proximal or distal tubular toxicity (19). Although acute renal tubular dysfunction that occurs during therapy often resolves prior to the next course, permanent and potentially progressive kidney damage may also occur (7,19).

b. Cisplatin and Carboplatin

Cisplatin (cis-diamminedichloroplatinum, CIS) is a heavy-metal compound used in the treatment of a large number of carcinomas including osteogenic sarcoma, Ewing's sarcoma, hepatoblastoma and germ cell tumours (12). Cisplatin induces acute changes in glomerular and tubular function (12). Proximal tubular toxicity causes hypomagnesaemia and hypocalcaemia, and glomerular damage can be noticed by reduced GFR (12,20). Cisplatin has been reported to induce long-term reduction in GFR and renal magnesium wasting (12). Womer *et al* (21) found a mean 8% decrease in GFR per 100 mg/m2 dose received. Use of CIS concurrently with other nephrotoxic agents, particularly IFO, increases the risk of renal injury (22).

Carboplatin (CARBO) is a structural analogue of CIS with a spectrum of activity similar to cisplatin. It is less nephrotoxic than cisplatin with myelosuppression being its major dose-limiting side effect (7). Carboplatin may be also associated with renal magnesium wasting and reduced GFR but the changes are less severe than those caused by cisplatin (12). Unlike cisplatin it is not transformed into toxic metabolites by renal tubule cells – hence its

decreased nephrotoxicity (7). Clinically important reductions in GFR and hypomagnesaemia are rare following carboplatin. Paradoxically, it is possible that the risk of renal insufficiency and tubulopathies is higher with carboplatin/ifosfamide than with cisplatin/ifosfamide combination therapy (22,24).

c. Methotrexate

Methotrexate (MTX) is a folate agonist that inhibits dihydrofolate reductase, the enzyme responsible for converting folic acid to reduced folate cofactors (12). High-dose methotrexate (HD-MTX) is commonly used in paediatric oncology in the treatment of acute lymphatic leukaemia (ALL), non-Hodgkin lymphoma (NHL), osteosarcoma and certain brain tumours (12). High-dose MTX (HDMTX), in which doses in the range of 1000-33,000 mg/m^2 are used in combination with leucovorin, is associated with acute renal dysfunction in 0-12.4% of patients with an overall incidence rate of 1.8% (25). The mechanism for MTX nephrotoxicity is postulated to be precipitation of the drug and metabolites within the renal tubular lumen. MTX related nephrotoxicity appears to be reversible, with a median time to recovery of renal function of 16 days (range 4-48 days) (25,26). There is a paucity of information regarding the long-term renal sequelae associated with MTX.

Radiation Therapy

Irradiation of the kidney can occur when the primary tumour is located in, or near, the kidney. In susceptible patients, radiation nephritis or radiation nephropathy arises after a latent period of 3-12 months and is manifest by varying degrees of hypertension, proteinuria, renal insufficiency and anaemia (15). Doses less than 18 gray (Gy) to the whole kidney appear to rarely cause severe or long-lasting renal injury while doses greater than 20

Gy result in significant nephropathy (27). In general, studies have shown that the risk for renal insufficiency is higher among children receiving higher doses of radiation (6,15).

Nephrectomy

Survivors of childhood cancer who have undergone nephrectomy are at risk for various complications including renal insufficiency, hyperfiltration injury, hypertension, and hydronephrosis (7). Compensatory hypertrophy of the remaining kidney is a well-documented finding after nephrectomy (28). Although this adaptation may initially increase glomerular filtration capacity, glomerulosclerosis and interstitial injury may ultimately lead to deterioration of renal function (7,26). For childhood cancer survivors, other nephrotoxic insults may also contribute to impaired renal function.

Supportive therapy

Supportive therapy is required due to prolonged periods of immune suppression from aggressive therapy with an increase in risk of nosocomial infections and neutropaenic sepsis (12). Some of the agents used include amphotericin B, nephrotoxic antibiotics such as amikacin and vancomycin and anti-viral agents such as cidofovir and foscarnet. Other agents such as cyclosporine A, for immunosuppressive therapy following stem cell transplantation, are also used. These agents can all cause a reduction in GFR and/or a distal tubulopathy with renal salt wasting, hypokalaemia, hypomagnesaemia and a loss of urine concentrating ability (12,29).

Amphotericin B is an antifungal agent used as treatment for patients with established or suspected fungal infections. Reported renal side effects include nephrotoxicity and

electrolyte abnormalities (hypokalaemia, hypomagnesaemia, and hyperchloraemic metabolic acidosis) (30,31). Severe renal failure is less common but the risks increase with diuretic-induced volume depletion or the concurrent administration of other nephrotoxins such as aminoglycoside antibiotics, cyclosporine A, nephrotoxic cancer chemotherapy and foscarnet (31). Amikacin, like other aminoglycosides, causes nephrotoxicity by inhibiting protein synthesis in renal cells. This mechanism specifically causes necrosis of cells in the proximal tubule, resulting in acute tubular necrosis which can lead to acute renal failure (32). Nephrotoxicity is an infrequent (5% of patients), and reversible, adverse effect of vancomycin but it may be potentiated by concomitant aminoglycoside therapy (33). The exact mechanism of vancomycin induced renal toxicity is not well defined (34).

Stem cell transplantation (SCT)

Stem cell transplantation is associated with several late effects, mainly depending on pre-transplantation conditioning therapy with or without total body irradiation (TBI), chemotherapy or organ manifestations of GVHD (12). Total bone irradiation is considered to be the principal cause of chronic SCT nephropathy, the clinical onset of radiation-induced nephropathy typically developing between 6 and 12 months after irradiation (15). It has been reported that 5-28% of paediatric long-term SCT survivors will develop chronic renal dysfunction (15,16). Patients treated with SCT have especially high risk for renal impairment since they have often already been treated with nephrotoxic drugs before SCT (12).

1.1.2 Evaluation of Childhood Cancer Survivors Treated with Nephrotoxic Therapy

Assessment of childhood cancer survivors for late renal sequelae is aimed at detection of hypertension or other evidence of chronic renal injury. The Children's Oncology Group Long

Term Follow Up (COG LTFU) Guidelines recommend baseline screening for asymptomatic survivors of potentially nephrotoxic therapy which include blood pressure measurement, serum electrolytes including calcium, magnesium and phosphate, serum urea and creatinine, and urinalysis (7).

The primary role of the kidney in the control of blood pressure is related to regulation of salt and water excretion in response to changes in extracellular fluid volume, and generation of agents which directly increase peripheral vascular resistance (34). Measurement of blood pressure as part of the routine physical examination allows detection of abnormal blood pressure which may be a pointer to underlying renal problem.

Finding significant proteinuria on urinalysis generates concern about renal damage from prior therapy or the acquisition of new renal disease (7). Persistently increased protein secretion is usually a marker of kidney damage. Standard urine dipsticks can be used in the screening of proteinuria (14).

Although glomerular filtration is only one component of renal function, it is often used as surrogate marker to assess overall renal function. Serum creatinine (SCr) is generally used as an indirect indicator of glomerular filtration rate (GFR) (7). This is based on the assumption that creatinine is primarily eliminated by glomerular filtration and that the production, and excretion, of creatinine are believed to be constant. However, a detectable change in the SCr is often seen much later after renal damage has occurred (12). Also, calculated GFR is most commonly estimated in children by using formulas based on the SCr and height,

however these formulae have not been shown to be accurate in all populations of children without underlying renal pathology (36,37).

Tubular damage in the kidneys may be accompanied by deranged serum electrolytes including magnesium, an alkaline urine pH and increased urinary excretion of phosphate, bicarbonate, sodium, potassium, glucose and amino acids. In addition, polyuria and hyperuricaemia may also complicate these finding (7,38).

After the baseline evaluation, annual follow-up is recommended (7). Progressive renal insufficiency, proteinuria, or hypertension should prompt referral to a nephrologist. Patients with a single kidney should be informed about potential risks to the remaining kidney (7). Patients at risk for renal sequelae should be counselled to avoid lifestyles that put them at risk for renal injury such as tobacco use, excessive NSAID use, excessive alcohol consumption, and dehydration. In addition, avoidance of obesity and treatment of hyperlipidaemia will also offer some renal protective effects (7).

1.2 Justification for the study

Despite concerted efforts by paediatric oncologists to offer a holistic and comprehensive post treatment follow up service, the health of the renal system is often neglected. Currently, at CMJAH, routine surveillance includes regular blood tests (full blood count, calcium, magnesium and phosphate, and urea, electrolytes and creatinine). However it does not always include routine blood pressure monitoring or urinalysis, even in patients known to have received nephrotoxic agents.

The serum creatinine, which is used as a marker for renal function, often lags behind deterioration in renal function, and significant damage to the kidneys may have already occurred before it increases to a point that will generate alarm.

There is little or no data on long term nephrotoxicity among children treated for cancer in South Africa and the findings of this study will give us some information on this topic and may also determine if changes should be made to the renal follow up protocol in these patients.

1.3 General aim

To determine renal side effects in children treated for childhood cancers in CMJAH.

Specific objectives

1. To document the different residual effects of cancer therapy on the renal system in this group of patients.
2. To determine the prevalence of these various renal side effects in this group.
3. To determine the factors associated with the above renal side effects in this group.

2. MATERIALS AND METHODS

2.1 Study Design

The study was a descriptive cross sectional study conducted at the paediatric oncology unit of CMJAH.

2.2 Study population

Children, between the age of 1 and 18 years, who had completed treatment at CMJAH and were being followed up at the paediatric oncology clinic of the hospital.

2.3 Selection criteria

Inclusion criteria

Children aged between 1 and 18 years at the oncology clinic at CMJAH who had completed treatment and were in remission.

Exclusion criteria

1. Children with evidence of renal impairment prior to diagnosis of cancer.
2. Children whose parents or caregivers refused consent.
3. Children who presented to the clinic for unscheduled non routine visits.
4. Children who fell outside the study age group criteria

2.4 Sample size

The sample size calculated for the study was 206, using the sample size determination for proportions (39) and a reference prevalence of a previous study of 15.9% (8). This target was not achieved on account of logistics and time constraints. Despite extending the period of data collection by 2 months and numerous efforts at calling-in patients, only 130 patients were able to be enrolled by the end of the time period allocated to data collection.

2.5 Data collection

All patients who met the selection criteria were recruited consecutively from the paediatric oncology clinic. Patients recruited had a general examination (performed by the principal investigator) with emphasis on anthropometry and blood pressure, and findings were recorded on a standard patient data capture sheet. Blood pressure was measured using a mercury sphygmomanometer. A urine sample was collected for each of the patients and a dipstick urinalysis was performed, the findings of which were also recorded on the data capture sheet. The data capture sheet was also used to collect patients' details with regard to details on the type of cancer diagnosed and available pre-treatment investigations and treatment. All other information about the patients was obtained from the patient records in the data base of the oncology unit of the paediatrics department at CMJAH.

Blood results of samples already routinely sent to the laboratory, as part of the current standard follow up protocol of the unit (full blood count, calcium, magnesium and phosphate, and urea, electrolytes and creatinine) were retrieved and recorded onto the data capture sheet.

No time limit in terms of post treatment duration for recruitment of patients was used. Patients with abnormal results were referred to the paediatric renal clinic at CMJAH for further evaluation. A sample of the data capture sheet used can be viewed in appendix A.

2.6 Definition of renal dysfunction

We have labelled the presence of any of the following "Renal Dysfunction" namely reduced eGFR, hypophosphataemia, hypomagnesaemia, proteinuria, haematuria, glucosuria and hypertension. Estimated GFR was calculated using the modified Schwartz formula (36) and eGFR <90 ml/min per 1.73m^2 was considered as abnormal as recommended by the Kidney Disease Outcomes Quality Initiative guidelines (40). Also, serum phosphate and magnesium levels of less than 0.9mmol/L and 0.7mmol/L respectively were considered as abnormal. Dipsticks for protein, blood and glucose were considered abnormal if they were ≥ 1+ when compared with the reference chart. Hypertension was defined by the patient having a systolic and/or diastolic blood pressure (BP) that was in the 95th percentile or higher for sex, age, and height (41).

2.7 Data analysis

All data were collated, checked and analysed using the STATA statistical package version 13. Continuous variables were described using mean and standard deviation. Categorical variables are presented as percentages. Chi Square test and Logistic Regression Analyses were used to test for the association between the outcomes and the various exposures. A

confidence interval of 95% was used and a p value of less than 0.05 was regarded as significant.

2.8 Ethics and consent

Ethical clearance was obtained from the human research ethics committee of the University of the Witwatersrand. (Ethics clearance certificate number: M130821)

Informed consent was obtained from the legal guardians of the patients included in the study and assent was obtained from children old enough to understand the study.

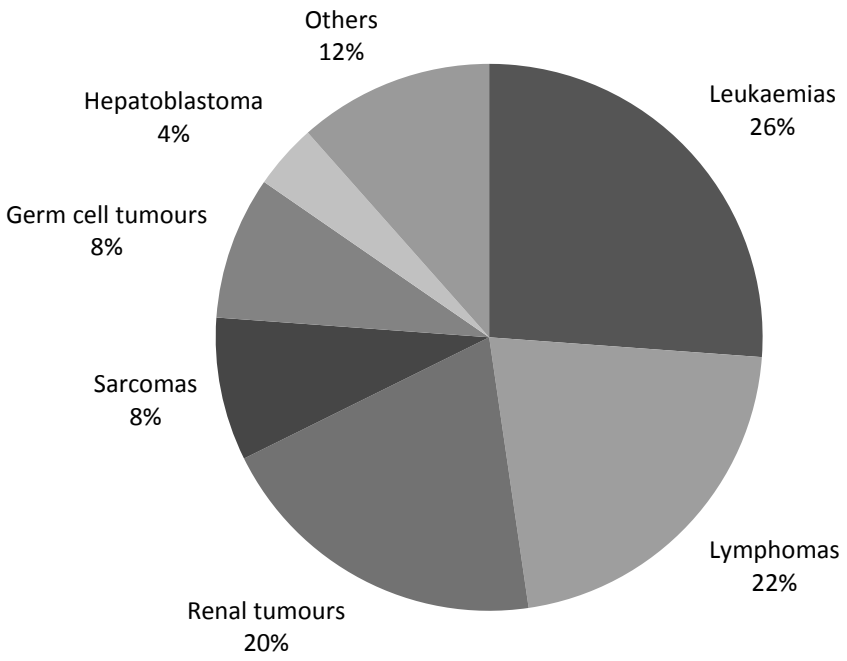
3. RESULTS

Between October 2013 and May 2014, 130 survivors of childhood cancer were recruited for the study. The male to female ratio was 1.13:1. The mean age of the children at the time of recruitment was 10.93 years ± 4.65 with a mean height and weight of 138.1cm ± 25.8 and 39.9Kg ± 21.7 respectively (Table 1). The leukaemias were the most prevalent group of childhood cancers treated among the group (Figure 1).

Table1. Descriptive characteristics of the childhood cancer survivors

Sex	**n=130**	**100%**
Male	69	53.08
Female	61	47.92
Age group (years)		
≤5	20	15.38
>5 - 10	39	30.00
>10 - 15	45	34.62
>15	26	20.00
Age at Diagnosis (years)		
<5	68	52.31
5 - <10	35	26.92
10 - <15	24	18.46
>15	3	2.30
Duration of treatment (months)		
1 – 6	36	27.69
>6 – 12	41	31.54
>12	53	40.77
Duration after treatment (years)		
<1	59	45.38
1 - <5	56	43.08
>5	15	11.54

Figure 1. Pie chart showing distribution of treated childhood cancers



The prevalence of renal dysfunction

Thirty four (26.15%) of the cohort had missing/incomplete results (pre-treatment) from the clinical records. They were excluded from the analysis. In the remaining patients, who had a complete set of records available, the various manifestations of renal dysfunction identified (both pre and post treatment) included; reduced glomerular filtration rate (GFR), hypomagnesaemia, hypophosphataemia, proteinuria, haematuria and hypertension. In addition to the above, glucosuria was also identified as one manifestation of renal dysfunction present pre-treatment (Table 2).

In total, 34 patients (26.15%) had at least one manifestation of renal dysfunction after completing treatment. The most prevalent manifestation of renal dysfunction detected was

decreased GFR which was present in 23 (17.69%) patients.. Hypomagnesaemia and hypophosphataemia were present in 8 (6.15%) and 6 (4.62%) of the patients respectively. Proteinuria, haematuria and hypertension had the least prevalence amongst the group (Table 2).

The prevalence of any form of renal dysfunction in the group was found to be higher pre-treatment as compared to the post-treatment (Table 3). The most prevalent form of renal dysfunction (both pre-treatment and post treatment) was reduced GFR (34.62% and 17.69% respectively).

When comparing the overall prevalence of renal dysfunction, pre and post-treatment, Table 4 demonstrates that 10 (18.5%) of the children who had no dysfunction prior to treatment were found to have at least one renal dysfunction post-treatment. Twenty five (59.5%) of the 50 patients who had renal dysfunction pre-treatment had no dysfunction post-treatment and 17 (40.5%) of those who had renal dysfunction pre-treatment still had at least one form of renal dysfunction.

Table 2. Prevalence of renal dysfunction in childhood cancer survivors pre-treatment

	n=130	%
Renal dysfunction (General)		
No	54	41.54
Yes	42	32.31
Data missing	34	26.15
Renal dysfunction (Cumulative)		
No problem	54	41.54
Single problem	37	28.46
2 problems	3	2.31
3 problems	1	0.77
4 problems	1	0.77
Data missing	34	26.15
Individual dysfunctions with proportions		
eGFR		
Normal	83	63.85
Low	45	34.62
Data missing	2	1.50
Magnesium		
Normal	123	94.62
Low	3	2.31
Data missing	4	3.08
Phosphate		
Normal	123	94.62
Low	3	2.31
Data missing	4	3.08
Urine Protein		
No	124	95.38
Yes	5	3.85
Data missing	1	0.77
Urine Blood		
No	124	95.38
Yes	6	4.62
Urine Glucose		
No	129	99.23
Yes	1	0.77
Hypertension		
No	95	73.08
Yes	5	3.85
Data missing	30	23.07

Table 3. Prevalence of renal dysfunction in childhood cancer survivors post-treatment

	n=130	%
Renal dysfunction (General)		
No	96	73.85
Yes	34	26.15
Renal dysfunction (Cumulative)		
No problem	96	73.85
Single problem	29	22.31
2 problems	4	3.08
3 problems	1	0.77
Individual dysfunctions with proportions		
eGFR		
Normal	107	82.31
Low	23	17.69
Magnesium		
Normal	122	93.85
Low	8	6.15
Phosphate		
Normal	124	95.38
Low	6	4.62
Urine Protein		
No	129	99.23
Yes	1	0.77
Urine Blood		
No	129	99.23
Yes	1	0.77
Urine Glucose		
No	130	100.00
Yes	0	0.00
Hypertension		
No	129	99.23
Yes	1	0.77

There was a significant statistical association between having renal dysfunction in general pre-treatment and then having it present post-treatment (p=0.02). Patients who had renal dysfunction pre-treatment in general were three times more likely to have renal dysfunction post-treatment (OR, 2.99; 95%CI, 1.19-7.53). (Table 5)

Table 4. Renal dysfunction in childhood cancer survivors pre and post-treatment

	Post-treatment		
	No	**Yes**	**Total**
Pre-treatment			
No	44	10	54
Yes	25	17	42
Missing data	27	7	34
Total	96	34	130

Table 5. Test of association between renal dysfunction pre and post-treatment, excluding the missing data.

		Post-treatment		
		No	**Yes**	**Total**
Pre-treatment	**No**	44	10	54
	Yes	25	17	42
	Total	69	27	96
Chi square = 5.64, p = 0.02			**OR = 2.99 (1.19-7.53), p = 0.02**	

Table 6. Univariate logistic regression analysis on the outcome variables (renal dysfunction)

	RENAL DYSFUNCTION					
	Decreased GFR n=23/130		Hypomagnesaemia n=8/130		Hypophosphataemia n=6/130	
	OR (95%CI)	P Value	OR (95%CI)	P Value	OR (95%CI)	P Value
EXPOSURE						
Ifosfamide (no/yes)	2.98 (1.13-7.88)	0.03	2.33 (0.52-10.41)	0.27	3.96 (0.75-20.81)	0.10
Carboplatinum (no/yes)	3.46 (1.19-10.12)	0.02	_a	_a	1.18 (0.13-10.68)	0.89
Cisplatinum	1.09 (0.28-4.16)	0.12	2.57 (0.47-13.99)	0.28	1.45 (0.16-13.30)	0.74
Ifosfamide + Carboplatinum (no/yes)	3.15 (1.48-6.71)	<0.01	1.05 (0.29-3.74)	0.94	2.31 (0.67-7.89)	0.18
Ifosfamide + Cisplatinum (no/yes)	1.86 (0.90-3.82)	0.09	2.15 (0.75-6.11)	0.15	2.31 (0.72-7.45)	0.16
Methotrexate (no/yes)	0.27 (0.09-0.84)	0.02	2.75 (0.63-12.07)	0.18	1.58 (0.31-8.17)	0.58
Nephrectomy (no/yes)	5.62 (2.10-15.03)	<0.01	_a	_a	_a	_a
TLS (no/yes)	2.39 (0.21-27.5)	0.49	_a	_a	_a	_a
Radiotherapy (no/yes)	1.03 (0.36-3.21)	0.89	0.53 (0.06-4.48)	0.56	1.98 (0.34-11.43)	0.45
Amikacin (no/yes)	0.9 (0.34-2.39)	0.83	0.68 (0.13-3.54)	0.65	0.41 (0.04-3.58)	0.42
Vancomycin (no/yes)	1.45 (0.51-4.11)	0.49	_a	_a	0.76 (0.08-6.74)	0.80
Amphotericin B (no/yes)	2.39 (0.21-27.51)	0.49	_a	_a	_a	_a
Duration of treatment (months)	0.96 (0.92-1.01)	0.40	1.03 (0.97-1.08)	0.34	0.99 (0.92-1.06)	0.73
Duration after treatment (years)	1.26 (1.07-1.47)	<0.01	0.60 (0.28-1.27)	0.18	0.78 (0.44-1.39)	0.40

_a :Not included in the logistic regression because of too few individuals with the exposure or the variable(dysfunction).

Table 6 demonstrates the individual exposures as independent risk factors for renal damage but only shows the results of the univariate logistic regression analyses for 3 of the outcome variables namely decreased GFR, hypomagnesaemia and hypophosphataemia. The remaining four variables namely proteinuria, haematuria, glycosuria and hypertension were not analysed as they were present in too few survivors to allow for the performance of any meaningful statistical analysis.

Table 7. Multivariate logistic regression for decreased GFR.

	Decreased GFR (n=23/130)	
	OR (95% CI)	**P value**
Exposure		
Nephrectomy	6.22 (1.85-20.98)	<0.01
Carboplatinum	3.97 (1.08-14.55)	0.04
Ifosfamide	5.06 (1.51-16.92)	<0.01
Duration after treatment (years)	1.20 (1.00-1.44)	0.05
Methotrexate	0.41 (0.10-1.77)	0.23

As can be seen in Table 6, decreased eGFR was the only outcome that had a significant association with some of the exposures. Use of ifosfamide (OR, 2.98; 95%CI, 1.13-7.88), carboplatinum (OR, 3.46; 95%CI, 1.19-10.12) and having had a nephrectomy (OR, 5.62; 95%CI, 2.10-15.03) had the strongest association with reduced eGFR. Survivors who had ifosfamide/carboplatinum combination therapy (OR, 3.15; 95%CI, 1.48-6.71) were more likely to develop decreased GFR when compared to survivors who had ifosfamide/cisplatinum combination therapy (OR, 1.86; 95%CI, 0.90-3.82). Duration after

treatment (OR1.26; 95%CI, 1.07-1.47) also had a significant association with decreased GFR. Patient who had methotrexate as part of their treatment were less likely to have decreased GFR (Table 6).

Table 7 shows a multivariate model of the adjusted exposures significant to decreased GFR. In Table 7 we see that decreased GFR was still significantly associated with nephrectomy, carboplatin, ifosfamide and the duration after treatment but not with methotrexate. Patient who had nephrectomy were six times more likely to have a decreased GFR after treatment (Table 7).

No treatment related exposures could be identified for the occurrence of hypomagnesaemia and hypophosphataemia.

4. DISCUSSION

The causes of long term renal complications in childhood cancer survivors are multifactorial and may be due to the tumour itself, the variety of treatment modalities used to treat the cancer treatment and/or nephrotoxic supportive measures used during therapy. The risk of developing long term manifestations of renal damage is thought to increase with increasing survival rates (4-16).

This study attempted to document, and analyse, the different residual effects of cancer therapy on the renal system in a group of post treatment survivors of paediatric cancer at CMJAH.

Looking at the breakdown of the primary diagnosis in this cohort of patients, the leukaemias were found to be the most prevalent (26%), followed by the lymphomas (22%). This is in keeping with the distribution of childhood cancers in general as reported by the South African childhood cancer registry (2).

After a median duration following completion of treatment of 2 years, the different manifestations of renal dysfunction in this cohort of patients included reduced glomerular filtration rate (GFR), hypomagnesaemia, hypophosphataemia, proteinuria, haematuria and hypertension. These findings are similar to renal problems described in previous studies of long term outcome of cancer survivors. In these studies, reduced renal function was defined

by a decrease in GFR (<90ml/min/1.73m^2) and tubulopathies were diagnosed if the patients had hypomagnesaemia, hypophosphataemia and/or glucosuria (12-14,42-46). Hypertension has also been described by Knijnenburg *et al* (14) as one of the adverse effects that may be present in cancer survivors.

The overall prevalence of renal dysfunction in this study was 26.15%. This falls within the range of most studies that looked at the long-term adverse effects of cancer treatment in childhood cancer survivors (13,14,42,45). It is much higher than the prevalence recorded in the Egyptian study of 15.9% (8). This discrepancy is most likely due to the fact that the Egyptian study looked mainly at acute renal problems in the survivors and documented acute renal failure as being the most prevalent finding. The finding of a higher prevalence of renal dysfunction than was reported in the Egyptian study further emphasises the need for long-term renal follow-up of childhood cancer survivors, as it implies that the risk of renal dysfunction may still be present many years after completion of treatment.

Decreased GFR was the most prevalent of all the manifestations of renal dysfunction screened for in this study (17.69%). In these patients who had a reduced GFR, all had only a minor reduction in GFR (60-90ml/min/1.73m^2) or Stage 2 Chronic Kidney Disease as described by the National Kidney Foundation (40). Oberlin *et al* (45) reported a higher prevalence of 21.5%. A possible explanation for this difference is that Oberlin's study recruited survivors who were at least five years post completion of treatment and, as stated earlier, the longer the survival the more likely the chances of finding some form of renal

dysfunction. The Iranian study (13) included patients that were less than 5 years post-treatment while the Netherlands study (14) recruited patients who were at least 5 years post treatment. Both studies reported lower prevalence of decreased GFR of 7.5% and 4.5% respectively. Only the Egyptian study (8) reported cases with severe reductions in GFR. These were patients who had experienced acute renal failure in the past and now some of them (7.6%) needed chronic renal replacement therapy.

Hyphosphataemia and hypomagnesaemia were found in our group but in lower number (4.62% and 6.15%) compared to decreased eGFR (17.69%). Although renal phosphate wasting has been associated with the use of ifosfamide, (47) no treatment specific exposures could be identified. Likewise no factors associated with hypomagnesaemia could be identified in this study. Other studies (13,14,42,45,46) did not report a significant finding of hyphosphataemia and hypomagnesaemia except for the study by Skinner *et al* (44). They reported a prevalence of hypomagnesaemia of 32% in cisplatin-treated patients and 17% in carboplatin-treated patients after a 10 year follow-up.

Hypertension, proteinuria and haematuria were the least prevalent manifestations of renal dysfunction detected in this study and no patient was found to have glucosuria. The Iranian and Netherlands study (13,14) both reported significant numbers of cases with hypertension and proteinuria, these being the most prevalent of all forms of renal dysfunctions described in their survivors. Also, Bardi *et al* (42) reported proteinuria as the major finding in their study. All these studies looked at long term survivors who were at least 5 years post-treatment. The differences in study population, treatment modality, treatment doses,

follow up duration and definition of outcome measures may explain the variations observed in the prevalence of the individual outcomes.

To my knowledge, no studies have looked at the presence of renal dysfunction in general pre treatment as a risk for renal dysfunction post treatment. About a third of the patients in this study had at least one form of renal dysfunction pre-treatment compared to only a quarter who had renal dysfunction post treatment. Patients who had renal dysfunction pre-treatment were three times more likely to have renal dysfunction post-treatment. This is an important finding as it implies that patients who have some form of renal dysfunction prior to starting therapy need careful long term follow up.

Various exposures were tested for significance with renal dysfunction. Only ifosfamide, carboplatinum and nephrectomy were found to be significantly associated with renal dysfunction, specifically with a decrease in GFR. Patients who had been exposed to ifosfamide or carboplatinum were three times more likely to have a decrease in GFR while patients who had undergone a nephrectomy were five times more likely to have a decreased GFR. Patients who had been exposed to combination treatment with ifosfamide/cisplatinum were twice as likely to develop renal dysfunction post treatment but those exposed to ifosfamide/carboplatinum were three times more likely to develop decreased GFR post treatment.

After adjusting for the various significant exposures, nephrectomy, carboplatin, ifosfamide and the duration after treatment, but not methotrexate, all had an independent impact on decreased GFR. Patients who had undergone a nephrectomy were six times more likely to have a decreased GFR after treatment.

The risk for renal tubular wasting of phosphate and magnesium increases with increasing cumulative dose of certain anticancer drugs, particularly ifosfamide (48,49,19). Stohr *et al* (46) reported an increase risk of 5.6 in patients treated with 24-60g/m^2 and an increased risk of 18.8 in patients treated with >60g/m^2 cumulative dose of ifosfamide. Skinner *et al* (19) also reported a higher prevalence of 20.7% in patients treated with a median dose of 62g/m2 of ifosfamide. Also, several studies have reported an increase risk of ifosfamide induced tubulopathy when combined with a platinum drug (50,51).

Even though in this study the total cumulative doses for the various treatments were not estimated, no significant relationship was found between any of the treatment exposures and hypophosphataemia and hypomagnesaemia.

Duration after treatment was also significantly associated with GFR. As the duration after treatment increased, the likelihood of having reduced GFR also increased slightly. This is in keeping with previous studies that showed a higher prevalence of renal dysfunction in long-term survivors (13,14,42,44,45).

Some of the limitations of this study include the fact that the total cumulative dose of anti-cancer treatment used in the patients was not estimated or associated with the outcomes and also that about a quarter of the survivors had missing results/data pre-treatment. Another limitation was the inability to clearly ascertain whether the survivors who had renal dysfunction pre-treatment and subsequently post-treatment had developed new renal dysfunction or just a progression of the existing renal dysfunction.

CHAPTER 5. CONCLUSION

This study describes the various forms of renal dysfunction observed in a cohort of childhood cancer survivors post-treatment, their prevalence and their associated factors. A significant number of the survivors had a decreased GFR while some of them had hypomagnesaemia and hypophosphataemia after a median follow-up post treatment of 2 years. Less common was the finding of proteinuria, haematuria and hypertension. In addition, ifosfamide, carboplatinum, and nephrectomy were significantly associated with a reduction in GFR. A significant finding was that of the strong association between pre-treatment and post-treatment renal dysfunction. Patients with the former were three times more likely to have the latter. This is very important in terms of decision making for individual patients with respect to selecting treatment modalities and dosages and also with respect to instituting nephro-protective measures to avoid further damage to the kidneys during and after treatment. Future research on this topic should focus on newly diagnosed patients. A prospective follow-up study of children undergoing therapy for childhood cancer, with frequent assessment during and after treatment would help clarify many of the study limitations alluded to above. Such studies could perhaps include the use of more sensitive markers to detect early renal problems as creatinine usually lags behind in estimation of renal damage.

Although it is gratifying that the degree of renal dysfunction detected in this study was minimal, the high prevalence implies that long-term follow-up in childhood cancer survivors, with reasonable attention to the renal system, should be recommended for all survivors of childhood cancer and not just those treated for renal tumours.

APPENDIX A: DATA COLLECTION SHEET

Study number								
Sex (M/F)								
Date of Birth								
Diagnosis								
At diagnosis								
Date at diagnosis								
Systolic BP(mm/Hg)								
Diastolic BP (mm/Hg)								
Weight (Kg)								
Height (cm)								
Bicarbonate (mmol/l)								
Creatinine (umol/l)								
Calculated GFR (mL/min/m^2)								
Calcium (mmol/l)								
Phosphate (mmol/l)								
Urinalysis (Y/N)								
Urine Ph								
Urine Protein								
Urine Blood								
Urine Glucose								
Treatment								
Date started treatment								
Date completed treatment								
Ifosfamide (Y/N)								
Cisplatin (Y/N)								
Carboplatin (Y/N)								
Methotrexate (Y/N)								
Amikacin (Y/N)								
Vancomycin (Y/N)								
Amphotericin B (Y/N)								
Cyclosporin (Y/N)								
Radiotherapy (Y/N)								
Nephrectomy (Y/N)								
Bone marrow transplant (Y/N)								
Tumour lysis syndrome(Y/N)								
Renal replacement therapy (Y/N)								
At data capture								
Date of data capture								
Systolic BP(mm/Hg)								
Diastolic BP (mm/Hg)								
Weight (Kg)								
Height (cm)								
Bicarbonate (mmol/l)								
Creatinine (umol/l)								
Calculated GFR (mL/min/m^2)								
Calcium (mmol/l)								
Phosphate (mmol/l)								
Urinalysis (Y/N)								
Urine pH								
Urine Protein								
Urine Blood								
Urine Glucose								

APPENDIX B: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Abdullahi Mudi & Prof Janet Poole

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130821

NAME: (Principal Investigator)	Dr Abdullahi Mudi & Prof Janet Poole
DEPARTMENT:	School of Public Health Medical School
PROJECT TITLE:	Renal Side Effects in Children who have Completed Treatment for Childhood Cancers at Charlotte Maxeke Johannesburg Academic Hospital, South Africa
DATE CONSIDERED:	30/08/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Cecil Levy
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/09/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 10/3/14

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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